REMARKS/ARGUMENTS

The final Office Action of June 26, 2008, has been carefully considered and these amendments and remarks are responsive thereto. Applicants' counsel wishes to thank Examiner Simmons and his Supervisor, Frederick Krass, for discussing the application on October 2, 2008. While no agreement on allowable subject matter was reached at that time, Applicants' counsel gained a greater appreciation for the Office's positions. The Office communication mailed October 21, 2008, includes an Interview Summary, which accurately sets forth the substance of the interview.

Claims 1, 10, 14, and 29 have been amended, and new claims 30 and 31 have been added. Claims 2-9, 12-13, 19-22, and 24-28 have been cancelled. No new matter has been added and the Applicants respectfully submit that the pending claims 1, 7, 10-11, 14-18, 23, and 29-31 are in condition for allowance.

Election/Restrictions and Rejoinder Practice

Claim 29 has been amended to so that it is directed to a process that has all of the features of product claim 1, as amended. Support for the amendments to claim 1 and 29 can be found in Table 1, on page 4, and in Table 4 on page 7 of the specification as originally filed. It is respectfully submitted that claim 29 be rejoined with claim 1. New claims 30 and 31 are directed to a process or composition wherein the metaxalone has a specific surface area per unit volume of more than about $2.5m^2/cm^3$. The surface area feature of new claims 30 and 31 correspond to the particle size feature of claims 1 and 29, as amended. The surface area feature of claims 30 and 31 correspond to the surface area of the metaxalone particles in the comparison testing with commercial metaxalone (Skelaxin) set forth in the specification as originally filed. Support for new claims 30 and 31 can be found at the second full paragraph on page 4 of the specification as originally filed.

Amendment to the Specification

The specification was objected to with respect to specific language added to the specification in the Response filed March 20, 2008, on the basis that the objected to language

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introduced new matter. To facilitate prosecution, the specification has been amended to delete the specific language objected to by the Examiner. Applicants understand that Examiner did not object to the other amendments to the specification filed on March 20, 2008, but only objects to the language that relates to enhanced bioavailability.

Rejections under 35 USC 103(a)

Claims 1, 3-5, 7-18, 23 and 27 were rejected under 35 U.S.C. § 103(a) as being unpatentable over Liversidge et al. U.S. Patent No. 5,145,684 in view of Scaife et al. U.S. Patent No. 6,407,128. Claims 1, 4-7, 15-18 and 23 were rejected under 35 U.S.C. § 103(a) as being unpatentable over Martin et al. U.S. Patent No. 4,344,934 in view of Scaife et al. U.S. Patent No. 6,407,128. The Applicants respectfully disagree and traverse the rejections.

Drug Absorption is Notoriously Unpredictable

Claim 1 has been amended to claim: "A pharmaceutical composition comprising metaxalone and at least one pharmaceutically acceptable excipient, characterized in that the pharmaceutical composition has a greater rate and extent of absorption as compared to the pharmaceutical composition of metaxalone described in New Drug Application No. 13-217 when orally administered to a patient on an empty stomach, wherein at least 99% of the metaxalone has a particle size not more than about 10μm in diameter. Independent method claim 29 has similar features as amended claim 1. Claim 1 has been amended to include the features of claim 27, and claim 27 has been cancelled.

Independent claim 29 has been amended to so that it is directed to a process that has features of the independent product claim 1, as amended.

New independent method claim 30 claims: "A method comprising orally administering to a patient a pharmaceutical composition comprising metaxalone and at least one pharmaceutically acceptable excipient, characterized in that the pharmaceutical composition has a greater rate and extent of absorption as compared to the pharmaceutical composition of metaxalone described in

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New Drug Application No. 13-217 when orally administered to a patient on an empty, wherein the metaxalone has specific surface area per unit volume of more than about $2.5m^2/cm^3$."

New independent method claim 31 claims: "A pharmaceutical composition comprising metaxalone and at least one pharmaceutically acceptable excipient, characterized in that the pharmaceutical composition has a greater rate and extent of absorption as compared to the pharmaceutical composition of metaxalone described in New Drug Application No. 13-217 when orally administered to a patient on an empty, wherein the metaxalone has specific surface area per unit volume of more than about $2.5m^2/cm^3$."

Support for the amendments to the claims and new claims 30 and 31 are recited in above in the section entitled "**Election/Restrictions and Rejoinder Practice.**"

The features upon which applicant relies are present in the pending claims.

The Office Action states that even if the claims are amended to include the feature "an increase in both rate and extent of absorption," the claims would have still been obvious to the skilled artisan because there is some predictability in accomplishing this method.

It is respectfully submitted that the Office Action is in error in interpreting the meaning of "reasonable expectation of success." This position is unsupported by any reasoning as to how there is any predictability at all. If one tosses a coin there is a 50% chance that you get a head or a tail. However, there is no predictability as to whether you will get heads or tails. Reasonable expectation of success is not the same as probability. Reasonable expectation of success requires some reason or an underpinning logic which would lead a person of ordinary skill in the art to expect a successful outcome. Here, there are several possible results when a composition is given on an empty stomach:

- Only the rate of absorption increases but extent of absorption is unaffected
- Only the extent of absorption increases but rate of absorption is unaffected
- Both the rate and extent of absorption are unaffected
- Both the rate and extent of absorption increase

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There is no particular reason for a person of skill in the art to expect that an increase in both the rate and extent of absorption is more likely than the other results. This is evidenced particularly because at least one method, *i.e.* that of Scaife, did not result in increase in both the rate and extent of absorption. In fact, the applicants submit that this outcome of both increase in rate and extent of absorption is less likely than an increase in only one of either the rate or extent of absorption.

Drug absorption is a notoriously unpredictable subject. In fact, there are prior findings where the extent of absorption has *decreased* upon grinding of the active ingredient. (Kahela, P et al, *Acta Pharm. Fenn.*, (April 1978, vol. 87, pp. 185-188. This and other references demonstrating variable results were cited in Applicants' response of March 20, 2008. The contrary result in Scaife (i.e., of decreased rate of absorption) is also ignored in the final Office Action. Where the prior art contains "apparently conflicting" teachings (i.e., where some references teach the combination and others teach away from it), each reference must be considered for its power to suggest solutions to an artisan of ordinary skill, considering the degree to which one reference might accurately discredit another. *Medichem, S.A. v. Rolabo, S.L.*, 437 F.3d 1157 (Fed. Cir. 2006). Therefore, Applicants' assertion that there is no reasonable expectation of success is based on facts which the Office Action ignores. On the other hand, the Office Action does not enumerate any reason or facts to support the contention that there is a predictability in achieving the result, i.e., that both the rate and extent of absorption would be increased. All the Office Action asserts "is some predictability in accomplishing the method." However, the ability to practice the method does not amount to predictability if the desired result cannot be conceived as more likely than other possible results. Obviousness does not require absolute predictability, however, *at least some degree of predictability is required.* See MPEP 2143.02:

> Evidence showing there was no reasonable expectation of success may support a conclusion of nonobviousness. *In re Rinehart*, 531 F.2d 1048, 189 USPQ 143 (CCPA 1976) (Claims directed to a method for the commercial scale production of polyesters in the presence of a solvent at superatmospheric pressure were rejected as obvious over a reference which taught the claimed method at atmospheric pressure in view of a reference

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which taught the claimed process except for the presence of a solvent. The court reversed, finding there was no reasonable expectation that a process combining the prior art steps could be successfully scaled up in view of unchallenged evidence showing that the prior art processes individually could not be commercially scaled up successfully.)

It is undisputed that Liversidge does not identify metaxalone or any drug similar to metaxalone in terms of chemical structure. Similarly, it is undisputed that Martin does not identify metaxalone or any drug similar to metaxalone in terms of chemical structure.

It is respectfully submitted that the Office Action does not establish a *prima facie* case of obviousness. At the time of the present invention, there was no suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to use metaxalone as disclosed in Scaife and modify it in a manner disclosed in Liversidge or Martin for the objectives of obtaining an increase in both the rate and extent of absorption of metaxalone on an "empty stomach." In addition, at the time of the present invention, there was no reasonable expectation of success in modifying Liversidge or Martin, and using metaxalone as disclosed in Scaife.

The Examiner states that he does not agree with Applicants' arguments in the Response of March 20, 2008, that the increase in Tmax of metaxalone in the secondary reference Scaife inherently means that the rate of absorption is therefore decreased. The Examiner states that his disagreement is "because Tmax is also dependent on excretion from the body where there is an equilibrium between absorption and excretion."

It is respectfully submitted that the Examiner's assertion that the reason that Tmax is different in the present invention from Skelaxin can also be related to excretion is technically incorrect. In other words, the Examiner is taking a position that Tmax is an incorrect measure of rate of absorption. The Examiner's position is incorrect. Example 2 of the present invention, describes a two-way cross over pharmacokinetic study. In these crossover pharmacokinetic study, healthy male volunteers were given the products. In the first week, half of the group, the first group, was given the first product and the other half, the second group, was given the second product. After a period of rest (referred to as a washout period), the first group was given the

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second product and the second group was given the first product. This design was used in comparative bioavailability studies to ensure that the measures of bioavailability result from differences in absorption rather than other pharmacokinetic parameters such as excretion or elimination. The United States Food and Drug Administration provides guidelines for these studies and accepts them as appropriate measures of bioavailability. The Examiner's position is contrary to what is widely accepted. Furthermore, the Examiner's assertion ignores several references recited by the applicants, for example, the Response of March 20, 2008, wherein applicants recited the following:

> "Tmax is a parameter closely related to the rate of absorption and may be used as a simple measure of rate of absorption. (*See* Remington's Pharmaceutical Sciences", 18th Edition, Mack Publishing Company, Easton, Pennsylvania, 1990, page 1455, submitted in an Information Disclosure Statement filed on October 13, 2006)."

With the present Response, applicants provide two (2) more peer review publications that support the use of Tmax as a measure of rate of absorption:

1. Tmax: An unconfounded metric for rate of absorption in single dose bioequivalence studies. Pharmaceutical Research, Vol. 13, No. 2, 1996, 324-328.
2. Why rate of absorption inferences in single dose bioequivalence studies are often inappropriate. Pharmaceutical research, Vol. 15, No. 2, 1998, 276-279.

The Examiner states that the primary reference(s) is relied upon to show how bioavailability is generally enhanced for drugs for which one desires to have enhanced oral bioavailability. The primary references, Liversidge and Martin, however, do not show how both the rate and extent of absorption of a specific drug, let alone metaxalone, can be increased. In fact, other references shows variable results are achieved depending on a specific drug at issue.

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The Secondary Reference, Scaife, Teaches Away From The Present Invention

The arguments made in the Office Action at page 8 with respect to secondary considerations of nonobviousness, i.e., the unexpected result of increased rate and extent of absorption when the metaxalone composition of the present invention is orally administered to a patient on an empty stomach, ignores the facts presented in the Response of March 20, 2008. For example, in the Response of March 20, 2008, applicants noted that "Metaxalone was first known through United States Patent No. 3,062,827 issued Nov. 6, 1962 and the product Skelaxin® (New Drug Application No. 13-217) was approved long before 1982 as indicated on the website of the USFDA, and yet persons of skill in the art never reached the results achieved by the present invention." The final Office Action of June 26, 2008, ignores the fact that persons of skill in the art worked to make Skelaxin® more bioavailable but did not reach the achievements made by the present invention. In the pharmaceutical product development arena it would be a reasonable assumption that a person of skill in the art will work towards the optimum formula that he/she can make from the available knowledge in the area. Thus the Examiner's contention that there is no evidence that persons of skill in the art were working on the problem is without merit. In fact, in Scaife et al., they considered an increase in extent of absorption to be an invention in the field. It can not be ignored that Scaife still failed to reach the result of an increase in both the "rate and extent of absorption," as claimed in the pending claims of the present application.

The Office Action concludes with the argument that "in addition to the reasonable expectation of successfully enhancing bioavailability of metaxalone, it would have also been obvious to make a composition having enhanced bioavailability without requiring the need to eat food and, therefore, making it easier to properly administer the drug." As shown above, however, there was no reasonable expectation of successfully increasing both the rate and extent of absorption with the oral administration of the claimed invention over that of the commercial product when orally administered to a patient on an empty stomach. Indeed, the primary references do not even mention metaxalone, and the secondary Scaife teaches away from the present invention. Additional references and secondary considerations further demonstrate the nonobviousness of the pending claims, as amended.

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U.S. PTO Memorandum of May 3, 2007, from Margaret A. Focarino, Deputy Commissioner for Patent Operations regarding the Supreme Court decision on *KSR Int'l Co. v. Teleflex, Inc.* stated: "[I]t remains necessary to identify the reason why a person of ordinary skill would have combined the prior art elements **in the manner claimed**." [Emphasis added] The Office Action fails to provide a reason why a person of ordinary skill would have combined the prior art elements **in the manner claimed**, because neither Liversidge nor Martin when combined with Scaife fills the vacuum in the prior art, the vacuum being the missing element of any suggestion, express or implicit, of an increase in both the rate and extent of absorption of metaxalone on an "empty stomach."

The Office Action is in error in omitting to consider the unexpectedness of the results, i.e., the increase in both the rate and extent of absorption of a specific drug, namely metaxalone, under the specific condition "that the patient is on an empty stomach." The result is unexpected, particularly in view of the fact that the only previous solution to the problem was recited in Scaife, which solution produced a contrary result (decreased rate of absorption). This error is the result of considering prior art references selectively rather than the prior art as a whole.

The pending claims 1, 7, 10-11, 14-18, 23, and 29-31 claim an increase in <u>both</u> the rate and extent of absorption of metaxalone as compared to Skelaxin® tablets (New Drug Application No. 13-217). The Applicants have in their earlier arguments presented that the effect of particle size reduction on the bioavailability (which has been defined as rate and extent of absorption in the present invention) of a drug on an empty stomach is not predictable. Pending claims 1, 7, 10-11, 14-18, 23, and 29 claim a pharmaceutical composition or method wherein at least 99 % of the metaxalone has a particular particle size. Pending claim 30 claims a pharmaceutical method wherein the metaxlone has a specific surface area per unit volume of more than about $2.5m^2/cm^3$ (which corresponds to the particular particle size claimed in independent claims 1 and 29).

The Office Action apparently concedes that Scaife et al. does not teach any particular values for the size of metaxalone particles in the dosage form nor name any particular solubilizing agent. Similarly, Scaife et al. does not teach any specific surface area per unit volume. It cannot be disputed that Scaife does not suggest any other form of metaxalone other

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than the conventional form described in the New Drug Application No. 13-217. The Office Action also does not dispute that Scaife discloses that providing metaxalone in conventional form with food is a satisfactory solution to Scaife's concerns with bioavailability.

One of ordinary skill in the art, having the benefit of Scaife's "food" solution, would not have been motivated at the time of the present invention to deviate from Scaife and use it in a method such as Liversidge or Martin with specific objectives of an increase in both rate and extent of absorption of metaxalone on an "empty stomach."

In the absence of a metaxalone specific prior art that would suggest that an increase in both the rate and extent of absorption of metaxalone on an empty stomach would be reasonably expected and in the presence of earlier failure (Scaife) to increase both the rate and extent of absorption of metaxalone, the findings of the present invention of increases in both the rate and extent of absorption of metaxalone on an empty stomach are indeed surprising. Metaxalone was first known through United States Patent No. 3,062,827 issued Nov. 6, 1962 and the product Skelaxin® (New Drug Application No. 13-217) was approved long before 1982 as indicated on the website of the USFDA, and yet persons of skill in the art never reached the results achieved by the present invention.

The Office Action overlooks important factors concerning nonobviousness of the claimed invention. The unexpected result of the present invention is increased rate and extent of absorption even when the composition is administered to a patient on an empty stomach. The prior art cited in the Office Action is general and does not suggest the present invention, which is directed specifically to metaxalone in a pharmaceutically acceptable solubility-improved form, or the unexpected results thereof. Further, the pharmaceutical arts are not predictable, particularly when complex biological systems are involved, and it is settled that it is improper to expect that the general teachings or teachings with reference to particular drug may be applied to another drug. *Accord,* MPEP 2164.03, noting predictable factors, such as mechanical or electrical elements, and unpredictable factors, such as most chemical reactions and physiological activity. *See also,* post-*KSR* cases, *Takeda Chem. Indus, Ltd. v. Alphapharm Pty., Ltd.*, 492 F.3d 1350 (Fed. Cir. 2007) (where there are no persuasive reasons to start with a lead composition and then modify it to form the claimed drug, the claimed drug will be found to be non-obvious), and

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Innogenetics, N.V. v. Abbott Laboratories, 512 F.3d 1363 (Fed. Cir. 2008) (merely listing of a number of prior art references and concluding with a stock phrase "to one skilled in the art it would have been obvious to perform the [claimed] method" is not articulated reasoning with some rational underpinning to support the legal conclusion of obviousness – knowledge of a problem and motivation to solve it are entirely different from motivation to combine particular references to reach the particular claimed method).

Thus, there is simply no reasonable expectation of success in achieving increased rate and extent of absorption provided in the teachings of prior arts for a particular form of metaxalone when dosed on an empty stomach over that of the commercially available form Skelaxin®.

It is not possible for one skilled in the art, and without stretching the hindsight theory to impermissible limits, to recognize that the composition of the present invention as claimed by the applicants produces unexpected advantages with regard to the rate and extent of absorption and bioavailability characteristics.

When the four factors in *Graham v. John Deere* are correctly applied in this case, it is apparent that the claimed invention is non-obvious over the cited art because neither Liversidge nor Martin when combined with Scaife fills the vacuum in the prior art, the vacuum being the missing element of any suggestion, express or implicit, of an increase in both the rate and extent of absorption of metaxalone on an "empty stomach." Scaife only succeeded in improving the extent of absorption of metaxalone but was unsuccessful in increasing the rate of absorption, as can be seen from the Scaife patent. However, it is clear that there is an error in Scaife in correctly recognizing whether in presence of food the rate of absorption increased or decreased. When recognition of the problem itself is unclear to a person of skill in the art, obviousness cannot be found. Conceptualization of the present invention involves recognizing the problem and formulating objectives of making improvements over prior art to provide the benefits of increased rate and extent of absorption of metaxalone on an empty stomach, *i.e.*, the patient is not inconvenienced with the requirement to take food along with the composition. This conceptualization is not the work of an ordinary artisan but the work of an inventor and the Office Action overlooks this factor because the Graham factors are not correctly applied. In making the assessment of differences between the prior art and the claimed subject matter, 35

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U.S.C.S. § 103 specifically requires consideration of the claimed invention as a whole. Inventions typically are new combinations of existing principles or features. The "as a whole" assessment of an invention under 35 U.S.C.S. § 103 requires a showing that an artisan of ordinary skill in the art at the time of invention, confronted by the same problems as the inventor and with no knowledge of the claimed invention, would have selected the various elements from the prior art and combined them in the claimed manner. *Princeton Biochemicals, Inc. v. Beckman Coulter, Inc.*, 411 F.3d 1332 (Fed. Cir. 2005).

Moreover, for long there was an unmet need for formulations of metaxalone that would provide increased rate and extent of absorption when given to a patient on an empty stomach. This unsolved problem has been successfully resolved by the present invention. Further, Scaife fails to recognize the problem overcome by the present invention. The present case is not unlike a "failure of others" when the problem is recognized but attempts to find a solution fail. Objective evidence, or "secondary considerations," of nonobviousness, such as "commercial success, long felt but unsolved needs, [or] failure of others" should be properly considered in an obviousness analysis. *Graham v. John Deere Co.*, 383 U.S. 1, 17-18, 86 S. Ct. 684 (1966).

Whereas administration of the Scaife composition with food leads to longer time to attain peak plasma level, the present invention does the opposite – *i.e.*, it takes less time to reach the peak plasma level in the present invention.

The Office Action does not respond to the argument that on p. 14 of the December 13, 2006 Response, and repeated in the argument on p. 12 of the July 2, 2007 Response that "whether it is in fact possible to obtain such an enhancement of both rate and extent of absorption of a particular drug cannot be predicted." The Office Action does not respond to the argument that "if for example one micronized drug shows improved bioavailability, it does not naturally extend or be extrapolated to metaxalone." The Office Action does not refute that these arguments are supported by the cited excerpts from "Remington's Pharmaceutical Sciences" at pages 14-15 of the December 13, 2006 Response. The Office Action does not respond to the argument that the cited teachings indicate "that there is no correlation between reduced particle size and bioavailability in the unpredictable pharmaceutical arts" and similar recognition in the U.S. Manual of Patent Examining Procedure (MPEP) 2164.03.

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The Office Action does not respond to the foregoing understanding of one of ordinary skill in the art. Instead, the Office Action takes a rigid approach by pointing to a teaching in Liversidge or Martin and contending that it would have been obvious to use Scaife with Liversidge or Martin to obtain a new form of metaxalone and that the new form of metaxalone would have both increased rate and extent of absorption on an empty stomach over that taught in the NDA.

Simply put, at the time of the present invention there was no reasonable expectation that metaxalone in a pharmaceutically acceptable solubility-improved form (e.g., micronized metaxalone) would have increased both rate as well as extent of absorption, as compared to the pharmaceutical composition of metaxalone corresponding to New Drug Application No. 13-217 when orally administered to a patient on an empty stomach.

The present case is analogous to *United States v. Adams*, 383 U.S. 39, 40 (1966), which was recently recited in *KSR v. Teleflex* – the analogy residing in the unexpected or unpredictable results in the present case and *Adams*. In *KSR*, the Court stated that "normal expected progressive innovation" is not an invention, but the present invention does not give something expected because the result as explained above is unpredictable. *KSR* therefore supports the patentability of the present invention particularly by reciting *Adams*.

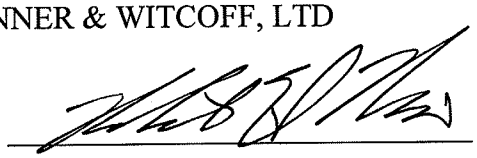
Conclusion

In view of the foregoing, it is respectfully submitted that the pending claims are in condition for allowance. The Examiner is invited to contact the undersigned should it be deemed helpful to facilitate prosecution of the application.

Respectfully submitted,

BANNER & WITCOFF, LTD

Date: October 27, 2008

By: 

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